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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/778,388	02/07/2001	Francis C. Szoka JR.	13054.01600	4514

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Nathan P. Koenig
Crosby, Heafey, Roach & May
P.O. Box 7936
San Francisco, CA 94120-7936

EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 11/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/778,388	SZOKA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *11 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,2,5-7 and 10-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 2, 5-7, 10-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/11/03 has been entered.

Claims 1, 2, 5-7, 10-52 are pending and under consideration in this Office Action.

Rejections Withdrawn

All rejections not reiterated can be considered to be withdrawn.

Drawings

Appicant filed informal drawings on that are acceptable for the purposes of examination.

Claim Objections

Claim 42 is objected to because it is ungrammatical. The word "conjugates" should be amended to "conjugate".

Claim 47 is objected to because "methylpyrolidone" is misspelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16 and 30-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 5, 10-14 are indefinite because it is unclear what is intended by the phrase, "the composition is non-polymeric". The specification does not define the term, but a reasonable interpretation would be a composition that comprises no polymers. So, because the claimed compositions must comprise hydrophilic polymers, the claim is indefinite

Claims 6, 7, and 19-29 are indefinite because a composition must comprise at least two elements, however the claims recite only an encapsulator. Further, the relationship between the encapsulator and the composition is unclear. The claims simultaneously require that the encapsulator is comprised by the composition, but that it also anchors the composition to the encapsulator. Because a composition must comprise two elements, but the instant claims recite only one (the encapsulator), it is unclear what is anchored by the encapsulator.

Claim 16 is indefinite because it is unclear what are the metes and bunds of a "dichloromethylmethyl ether derivative". The specification provides no limiting definition and it is unclear to what extent atoms can be added to, subtracted from, or substituted in dichloromethylmethyl ether and result in what Applicant considers a "derivative".

Claims 30-52 are indefinite because they recite "the hydrophobic portion" without antecedent basis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 6, 7, 15, 16, 19-21, 24, 25, 30, 31, 34, 38, 39, 42, and 50-52 are rejected under 35 U.S.C. 102(e) as being anticipated by Nantz (US Patent 6,200,599, issued 3/15/01).

Nantz teaches lipid formulations (liposomes, micelles, lipidic aggregates) comprising ortho ester lipids with a hydrophobic lipidic portion joined to a hydrophilic headgroup comprising an ammonium ion, and methods of delivering the composition to cells in vivo under conditions that result in acid catalyzed hydrolysis of the orthoester, and destabilization of the aggregate. See e.g. column 2, lines 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note that R2 in Formula I at column 2 may be an alkoxy group, thereby meeting the limitation that the hydrophobic group must be attached to the thioester by an oxygen atom. The lipid of the composition may comprise a targeting antibody attached to a hydrophilic polymer. See column 12, lines

51-60. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31. Nantz also teaches that the lipid may be prepared as a powder prior to rehydration and administration. See e.g. column 20, lines 44-56, and column 23, lines 7-15.

Claims 16, 30, 31, 34, and 35 are included in this rejection because the composition of Nantz appears to be substantially identical to that claimed. "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing Applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Response to Arguments

Applicant's arguments filed 7/18/03 have been fully considered but they are not persuasive.

Applicant argues that the instant claims distinguished over Nantz because the hydrophobic portion is attached to the orthoester via an oxygen and not a carbon. Applicant's attention is directed to column 2, lines 44-61 wherein Nantz discloses that an orthoester may be formed in which A and A1 can be oxygens, and the third oxygen is supplied by a C1-C18 alkoxy group. Thus the structure of Nantz anticipates the structure of the instant claims, and absent evidence to the contrary would have similar hydrolysis characteristics.

Claims 1, 2, and 10, stand rejected under 35 U.S.C. 102(b) as being anticipated by Klaveness et al (US Patent 6,106,806, issued 8/22/00).

Klaveness teaches gas-containing ultrasound contrast agents that are vesicular in nature and composed of polymerizable or crosslinkable units of the general formula $[(X)_p(R^{10})_q]B$, wherein X is a hydrophilic group, R^{10} is a hydrophobic group, and B is a crosslinker. See abstract; column 6, lines 1-20; and column 6, line 62 to column 7, line 7. Additional groups $[(X)_p(R^{10})_q]B$ may be crosslinked to a polymer of groups $[(X)_p(R^{10})_q]B$. The hydrophilic group may be a polyethylene glycol and may comprise a cationic quaternary amine. See column 6, lines 52-61, and column 7, lines 27-29, and column 14, lines 7-14. The hydrophobic group may be for example, cholesterol, acylphosphatidylserine, or acylphosphatidylcholine. See column 7, lines 7-14. The crosslinker may be an ortho ester. See column 6, lines 48-51. Formation of ortho ester crosslinks between these groups would necessarily result in compounds in which hydrophilic groups can be separated from hydrophobic groups by acid hydrolysis of an

ortho ester. Because the compositions of Klaveness comprise a gas that is not a monomer of the vesicle polymers, the compositions as a whole are not polymeric and Klaveness anticipates the claims. It is suggested that claim 1 should be amended similarly to claim 19 to require that the hydrophobic portion cannot be polymeric.

Response to Arguments

Applicant's arguments filed 7/18/03 have been fully considered but they are not persuasive.

Applicant argues that the compositions of Klaveness are polymeric. As noted above under 112, second paragraph rejections, it is un clear what is intended by "non-polymeric" in the claims. In any event , the composition of Klaveness comprises gas molecules that are not covalently linked to any polymer, so the composition as a whole is non-polymeric. This would be consistent with Applicant's apparent characterization of the composition of claim 1 as non-polymeric, even though it comprises hydrophilic polymers.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness et al (US Patent 6,106,806, issued 8/22/00) in view of Na et al (US Patent 5,447,710, issued 9/5/95.

The teachings of Klaveness are detailed above. Briefly, Klaveness teaches gas-containing ultrasound contrast agents that are vesicular in nature and composed of polymerizable or crosslinkable units of the general formula $[(X)_p(R^{10})_q]B$, wherein X is a hydrophilic group, R^{10} is a hydrophobic group, and B is a crosslinker. See abstract; column 6, lines 1-20; and column 6, line 62 to column 7, line 7. Additional groups $[(X)_p(R^{10})_q]B$ may be crosslinked to a polymer of groups $[(X)_p(R^{10})_q]B$. Polyethylene glycol may be attached to the surface of the vesicle by attachment to the lipid. See e.g. column 14, lines 7-14.

Klaveness does not teach polyethylene glycol having a molecular weight from 200-20,000.

Na teaches that the surfaces of contrast agents should be modified by polyethylene glycol of molecular weight above 4000.

It would have been obvious to one of ordinary skill in the art to use polyethylene glycol having a molecular weight from 200-20,000 in the invention of Klaveness. MPEP 2144.09 states that a prima facie case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities. "An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." In re Payne, 606 F.2d 303, 313,

203 USPQ 245, 254 (CCPA 1979). See In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (discussed in more detail below) and In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991). Compounds which differ regularly by the successive addition of the same chemical group are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). See also In re May, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978).

Thus the invention as a whole was *prima facie* obvious.

Claims 1, 2, 5, 6, 7, 10, 15, 16, 19-22, 24-32, 34-36, 38, 39, 42, 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zalipsky et al (US patent 5,395,619, issued 3/7/95) in view of Nantz (US Patent 6,200,599, issued 3/15/01), and Unger et al (US Patent 6,028,066 issued 3/31/98) and Unger et al et al al (US Patent 6,028,066, issued 2/22/00).

Zalipsky teaches a method for making lipid-hydrophilic polymer conjugates capable of incorporation into liposomes, for use in increasing liposome circulation time in vivo. The lipid may be any lipid that is capable of forming a liposome by itself, or can be stably incorporated into a liposome. The polymers include polyethylene glycol, polyvinylpyrrolidone, polymethyloxazoline, and polyethyloxazoline. See abstract, and e.g. column 10, lines 67 and 68. The polymers may comprise a targeting ligand. See column 10, lines 39-52.

Zalipsky does not teach linkage of the hydrophobic and hydrophilic groups by an orthoester; the particular hydrophobic groups distearoylglycerol, dimyristoylglycerol, dipalmitoylglycerol, cholesterol, ceramides, phosphatidylcholine, phosphatidylserine, phosphatidylglycerol, cholesterol sulfate, DOTAP, or DOTMA; or the particular targeting ligands hyaluronan, peptides, receptor antagonists, carbohydrates, protein hormones or cytokines attached to the hydrophilic polymer.

Nantz teaches the design and use of lipid aggregates designed to be destabilized by a decrease in pH for the purpose of improved DNA release from endosomes. See e.g. column 2, lines 13-42. The central element of the invention is an amphipathic molecule comprising an acid labile orthoester linkage that connects a hydrophobic portion to a hydrophilic portion. See abstract, column 2, lines 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note that R2 in Formula I at column 2 may be an alkoxy group, thereby meeting the limitation of claim 19 that the hydrophobic group must be attached to the thioester by an oxygen atom. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31.

Unger teaches that distearoylglycerol, dimyristoylglycerol, dipalmitoylglycerol, cholesterol, ceramides, phosphatidylcholine, phosphatidylserine, phosphatidylglycerol, cholesterol sulfate, DOTAP, and DOTMA are lipids that useful in the formation of liposomes. See e.g. column 23, line 35 to 53, column 24, lines 2 and 3, and column 29, lines 49-52. Unger teaches that lipid vesicles can be stabilized by including hydrophilic polymers such as polyethylene glycol or polyvinylpyrrolidone. The polymer may have a molecular weight from about 400 to about 100,000. Unger exemplifies

distearoylphosphatidyl ethanolamine PEG 5000. The polymer-conjugated lipid may be present in the vesicle at from 8-15% of the total lipid. See column 39, lines 15-60. Unger also teaches a variety of targeting ligands including hyaluronan, peptides, receptor antagonists, carbohydrates, protein hormones and cytokines that can be attached to the lipid via the hydrophilic polymer. See column 48, lines 11-16, 20-22, 39-42, and 62-65.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Zalipsky by using a phosphodiester linkage to attach hydrophilic polymers to a hydrophobic group in order to improve DNA release from endosomes as taught by Nantz. It would have been obvious to use any of the hydrophobic or targeting groups taught by Unger. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the lipids of Unger are recognized as suitable for forming and or stabilizing liposomes, and are equivalent to the lipids of Zalipsky that can form, or be stably incorporated into, liposomes. Similarly the targeting ligands are

art-recognized equivalents inasmuch as it recognized that they can be attached to lipids via hydrophilic polymers.

Claim 22 is included in this rejection because the lipid composition of the liposomes is recognized as a variable that is optimized by those of ordinary skill in the art. For example, Unger teaches a variety of proportions of lipid components, including a PEG5000- modified distearoyl-glycerolipid lipid from 8-15% of the total lipid of a vesicle. It would have been obvious to use methoxypolyethylene glycol 2000 diorthoester-distearoyl glycerol in an amount from 3-15% of the total lipid because: Applicant admitted on the record in Paper No. 5, page 1, that methoxypolyethylene glycol is an art recognized equivalent of PEG; Unger teaches that a range of PEGs overlapping the recited "2000" may function in the invention, and that glycerol distearate is a lipid that is useful for formation of liposomes; Zalipsky teaches that any lipid useful for forming liposomes may be modified with a hydrophilic polymer such as PEG; and Nantz teaches the improvement of using an orthoester linker to improve DNA delivery. Note that each of the hydrophilic polymers of Zalipsky has a terminal hydroxyl that could server in formation of the alkoxy group of Nantz, meeting the limitation of instant claim 19 requiring orthoester attachment through an oxygen atom.

Thus the invention as a whole was *prima facie* obvious.

Claims 19, 25, 30, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nantz (US Patent 6,200,599, issued 3/15/01) in view of Huang et al (US Patent 6,008,202 issued 12/28/99).

Nantz teaches lipid formulations (liposomes, micelles, lipidic aggregates) comprising ortho ester lipids with a hydrophobic lipidic portion joined to a hydrophilic headgroup comprising an ammonium ion, and methods of delivering the composition to cells in vivo under conditions that result in acid catalyzed hydrolysis of the orthoester, and destabilization of the formulation. See e.g. column 2, lines 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note that R2 in Formula I at column 2 may be an alkoxy group, thereby meeting the limitation that the hydrophobic group must be attached to the thioester by an oxygen atom. The lipid of the composition may comprise a targeting antibody attached to a hydrophilic polymer. See column 12, lines 51-60. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31.

Nantz does not teach liposome compositions comprising the lipids phosphatidic acid, DDAB, or cholesteryl hemisuccinate.

Huang teaches that phosphatidic acid, DDAB, or cholesteryl hemisuccinate are lipids that useful in the formation of liposomes. See e.g. column 10, line 56, and column 12, lines 14-21. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness.

See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was *prima facie* obvious.

Claims 19, 25, 30, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nantz (US Patent 6,200,599, issued 3/15/01) in view Sankaram et al (US Patent 5,993,850 issued 11/30/99).

Nantz teaches lipid formulations (liposomes, micelles, lipidic aggregates) comprising ortho ester lipids with a hydrophobic lipidic portion joined to a hydrophilic headgroup comprising an ammonium ion, and methods of delivering the composition to cells in vivo under conditions that result in acid catalyzed hydrolysis of the orthoester, and destabilization of the formulation. See e.g. column 2, lines 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note that R2 in Formula I at column 2 may be an alkoxy group, thereby meeting the limitation that the hydrophobic group must be attached to the thioester by an oxygen atom. The lipid of the composition may comprise a targeting antibody attached to a hydrophilic polymer. See column 12, lines 51-60. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31.

Nantz does not teach liposome compositions comprising cardiolipid or squalene.

Sankaram teaches cardiolipin and squalene are useful in the formation of liposomes. See e.g. column 7, lines 47-57. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other,

while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945).

Thus the invention as a whole was *prima facie* obvious.

Claims 19, 25, 30, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nantz (US Patent 6,200,599, issued 3/15/01) in view Sprott et al (US Patent 6,132,789, issued 10/17/00).

Nantz teaches lipid formulations (liposomes, micelles, lipidic aggregates) comprising ortho ester lipids with a hydrophobic lipidic portion joined to a hydrophilic headgroup comprising an ammonium ion, and methods of delivering the composition to cells in vivo under conditions that result in acid catalyzed hydrolysis of the orthoester, and destabilization of the formulation. See e.g. column 2, lines 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note that R2 in Formula I at column 2 may be an alkoxy group, thereby meeting the limitation that the hydrophobic group must be attached to the thioester by an oxygen atom. The lipid of the composition may comprise a targeting antibody attached to a hydrophilic polymer. See column 12, lines

51-60. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31.

Nantz does not teach compositions comprising coenzyme Q.

Sprott teaches that coenzyme Q when incorporated into liposomes increases the delivery of associated compounds. See e.g. column 4, lines 32-44, thus one would have been motivated to include it in the liposomal compositions of Nantz.

Claims 1, 2, 5, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zalipsky et al (US patent 5,395,619, issued 3/7/95) in view of Nantz (US Patent 6,200,599, issued 3/15/01), and Haynes et al (US Patent 5,015,483 issued 5/14/91).

Zalipsky teaches a method for making lipid-hydrophilic polymer conjugates capable of incorporation into liposomes, for use in increasing liposome circulation time in vivo. The lipid may be any lipid that is capable of forming a liposome by itself, or can be stably incorporated into a liposome. The polymers include polyethylene glycol, polyvinylpyrrolidone, polymethyloxazoline, and polyethyloxazoline. See abstract, and e.g. column 10, lines 67 and 68.

Zalipsky does not teach linkage of the hydrophobic and hydrophilic groups by an orthoester, or the hydrophobic groups tocopherol, ceramides, or cholesterol.

Nantz teaches the design and use of lipid aggregates designed to be destabilized by a decrease in pH for the purpose of improved DNA release from endosomes. See e.g. column 2, lines 13-42. The central element of the invention is an amphipathic

molecule comprising an acid labile orthoester linkage that connects a hydrophobic portion to a hydrophilic portion. See abstract.

Haynes teaches that lipids that can be incorporated into liposomes include tocopherol, ceramides, and cholesterol. See column 10, lines 4-13, and column 14, lines 3-23.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Zalipsky by using a phosphodiester linkage to attach hydrophilic polymers to a hydrophobic group in order to improve DNA release from endosomes. It would have been obvious to use any of the hydrophobic groups taught by Haynes. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the lipids of Haynes are recognized as suitable for forming and or stabilizing liposomes, and are equivalent to the lipids of Zalipsky that can form, or be stably incorporated into, liposomes.

Thus the invention as a whole was *prima facie* obvious.

Claims 1, 2, 5, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zalipsky et al (US patent 5,395,619, issued 3/7/95) in view of Nantz (US Patent 6,200,599, issued 3/15/01), and Sprott et al (US Patent 6,132,789, issued 10/17/00).

Zalipsky teaches a method for making lipid-hydrophilic polymer conjugates capable of incorporation into liposomes, for use in increasing liposome circulation time in vivo. The lipid may be any lipid that is capable of forming a liposome by itself, or can be stably incorporated into a liposome. The polymers include polyethylene glycol, polyvinylpyrrolidone, polymethyloxazoline, and polyethyloxazoline. See abstract, and e.g. column 10, lines 67 and 68.

Zalipsky does not teach linkage of the hydrophobic and hydrophilic groups by an orthoester, or the hydrophobic group coenzyme Q.

Nantz teaches the design and use of lipid aggregates designed to be destabilized by a decrease in pH for the purpose of improved DNA release from endosomes. See e.g. column 2, lines 13-42. The central element of the invention is an amphipathic molecule comprising an acid labile orthoester linkage that connects a hydrophobic portion to a hydrophilic portion. See abstract.

Sprott teaches that coenzyme Q is a lipid that can be that can be incorporated into liposomes, and which can promote phagocytosis of the liposomes. See e.g. column 3, lines 27-46.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Zalipsky by using a phosphodiester linkage to attach hydrophilic polymers to a hydrophobic group in order to improve DNA release from

endosomes. It would have been obvious to use any of the hydrophobic groups taught by Sprott, including coenzyme Q. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the lipids of Sprott are recognized as suitable for forming and or stabilizing liposomes, and are equivalent to the lipids of Zalipsky that can form, or be stably incorporated into, liposomes.

Thus the invention as a whole was *prima facie* obvious.

Claims 38 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nantz (US Patent 6,200,599, issued 3/15/01) in view of Eppstein et al (US Patent 4,897,355, issued 1/30/90).

Nantz teaches lipid formulations (liposomes, micelles, lipidic aggregates) comprising ortho ester lipids with a hydrophobic lipidic portion joined to a hydrophilic headgroup comprising an ammonium ion, and methods of delivering the composition to cells in vivo under conditions that result in acid catalyzed hydrolysis of the orthoester,

and destabilization of the . See e.g. column 2, lines 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note that R2 in Formula I at column 2 may be an alkoxy group, thereby meeting the limitation that the hydrophobic group must be attached to the thioester by an oxygen atom. The lipid of the composition may comprise a targeting antibody attached to a hydrophilic polymer. See column 12, lines 51-60. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31.

Nantz does not teach administration of the lipid formulations as a dry powder.

Eppstein teaches that lipid formulations may be prepared and administered as powders. See column 13, lines 18-20.

It would have been obvious to administer the composition of Nantz as a powder because, in view of the teachings of Eppstein, it was routine in the art at the time of the invention to do so.

Thus the invention as a whole was *prima facie* obvious.

Claims 38, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nantz (US Patent 6,200,599, issued 3/15/01) in view of Eppstein et al (US Patent 4,897,355, issued 1/30/90) and Lishko et al (US Patent 5,753,263, issued 5/19/98).

Nantz teaches lipid formulations (liposomes, micelles, lipidic aggregates) comprising ortho ester lipids with a hydrophobic lipidic portion joined to a hydrophilic headgroup comprising an ammonium ion, and methods of delivering the composition to cells in vivo under conditions that result in acid catalyzed hydrolysis of the orthoester,

and destabilization of the formulation. See e.g. column 2, lines 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note that R2 in Formula I at column 2 may be an alkoxy group, thereby meeting the limitation that the hydrophobic group must be attached to the thioester by an oxygen atom. The lipid of the composition may comprise a targeting antibody attached to a hydrophilic polymer. See column 12, lines 51-60. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31.

Nantz does not teach rehydration of a drug-containing dry powder liposome formulation prior to administration.

Eppstein teaches that lipid formulations may be prepared and administered as powders. See column 13, lines 18-20.

Lishko teaches lyophilization of liposome compositions for storage, followed by rehydration.

It would have been obvious to one of ordinary skill in the art at the time of the invention to lyophilize the compositions of Nantz in order to store them, and to rehydrate them prior to use. One would have been motivated to do so because one of ordinary skill in the art appreciates that it is efficient to make large quantities of a composition which can be conveniently stored and used when needed. Given the teachings of Lishko one of ordinary skill in the art could have lyophilized and rehydrated the compositions of Nantz with a reasonable expectation of success. The decision to do so is design choice made by one of ordinary skill in the art

Thus the invention as a whole was *prima facie* obvious.

Claims 42 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nantz (US Patent 6,200,599, issued 3/15/01) in view of Needham, US Patent 5,827,533 (issued 10/27/98).

Nantz teaches the design and use of lipid aggregates designed to be destabilized by a decrease in pH for the purpose of improved DNA release from endosomes. See e.g. column 2, lines 13-42, column 2, lines 44 to column 3, line 18, column 5, lines 53-56, and column 12, lines 13-17. Note that R2 in Formula I at column 2 may be an alkoxy group, thereby meeting the limitation that the hydrophobic group must be attached to the thioester by an oxygen atom. The lipid of the composition may comprise a targeting antibody attached to a hydrophilic polymer. See column 12, lines 51-60. The composition may comprise the fusogenic lipid DOPE. See column 9, lines 24-31.

Nantz does not teach a method of combining an encapsulator suspension with a dry film of a lipidic ortho ester composition.

Needham teaches a method of encapsulating micelles in lipid vesicles wherein lipids were dried to a film and rehydrated with a suspension of micelles containing an active agent.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Needham by using the lipids of Nantz in either or both of the micelle and the vesicle. One would have been motivated to do so in order to improve intracellular release of the active agent upon entry into the endosomal pathway.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Claims 11-14, 17, 18, 23, 33, 37, 43, 44, and 46-49 are free of the art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached at 703-306-3217. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.